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Editorial

Ca^{2+} signaling mechanisms of cell survival and cell death: An introduction

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ABSTRACT

Ca^{2+} regulates many steps in cell death mechanisms, and is potentially involved in all types of cell death. Moreover, virtually all elements of the cellular Ca^{2+} toolbox seem to contribute to remodeling of the Ca^{2+} signaling machinery during cell death processes. As expected from the ubiquitous nature of Ca^{2+} signaling, these mechanisms are operative in all cell types, and their malfunction may lead to a wide diversity of pathological implications. The contributions in this Special Issue deal with many different aspects of the relation between Ca^{2+} signaling and cell death. They illustrate the complexity of this relation, and importantly they give an outlook on potential new therapeutic targets for treatment of diseases connected to defects in cell death pathways.

The importance of cellular Ca^{2+} signaling in cell death and survival has already been recognized in very early experiments showing the toxicity of excess Ca^{2+} influx or receptor overstimulation. An overview of the overwhelming amount of experimental data that illustrate the general importance of these early observations is given in the first contribution to this Special Issue by B. Zhivotovsky and S. Orrenius and has been discussed in several excellent reviews [1–10]. The full complexity of the interrelation between Ca^{2+} signaling and cell death is evident at different levels. At first, it became increasingly clear that Ca^{2+} regulates many steps in the mechanisms for cell death initiation, in the downstream effects of cell death and in cell death recognition by macrophages. Secondly, virtually all elements of the cellular Ca^{2+} toolbox seem to contribute to remodeling of the Ca^{2+} signaling machinery during cell death processes [2,11]. Thirdly, Ca^{2+} signaling is potentially involved in all types of cell death, and moreover it seems to play a pivotal role in controlling cellular life-or-death decisions and in the choices between apoptosis, necrosis or autophagy. Finally, as expected from the ubiquitous nature of Ca^{2+} signaling [11], these mechanisms are operative in all cell types, and their malfunction may lead to a wide diversity of pathological implications.

An important breakthrough with respect to Ca^{2+}-dependent apoptosis was obtained after it became clear that there was a "privileged" Ca^{2+} transfer from the ER to the mitochondria due to signaling micro-domains in close contact sites between these two organelles (for recent reviews: [12–14]). Within the ER-mitochondrial micro-domain (called MAM for mitochondria-associated membrane) Ca^{2+} concentration exceeds 10 μM, which explains the very efficient mitochondrial Ca^{2+} uptake via an apparently low-affinity Ca^{2+} transporter [15]. The protein complex associated with the MAM was shown to be organized around two abundant ion channels, the IP_3R in the ER and VDAC in the outer mitochondrial membrane (OMM) [5]. The IP_3R was found to be physically connected with VDAC-1 in the OMM via GRP75, an assembly which couples the IP_3R to the mitochondrial Ca^{2+}-uptake machinery [5]. The VDAC-GRP75-IP_3R protein complex in the MAM provides a crucial interface for ER-to-mitochondria Ca^{2+} signaling in one direction and for ATP and redox signaling in the reverse direction. The IP_3R is a sensor and integrator of the cytoplasmic and luminal ER environments, converting these parameters into a mitochondrial Ca^{2+} signal that functions as an important determinant for subsequent cell fate. As a consequence, a number of cellular regulators of IP_3R activity are directly involved in cell death [16,17]. As extensively discussed by the contribution of C. Distelhorst and M. Bootman in this Special Issue, the role of the IP_3R in cell death is closely connected to regulation of IP_3-induced Ca^{2+} release (IICR) by Bcl-2-family proteins either directly [18,19] or indirectly via effects on the ER store content [20,21]. Recent evidence points to differential properties of Bcl-2, Bcl-XL and other anti-apoptotic proteins, and suggests a specialized role in the fine tuning of the mitochondrial Ca^{2+} signal. While Bcl-2 was shown to physically interact with the IP_3R and thereby inhibit IICR and pro-apoptotic Ca^{2+} signaling to the mitochondria [22], a quite different behavior was found for the related anti-apoptotic Bcl-XL, which sensitized IP_3Rs to basal [IP_3] and induced small oscillatory Ca^{2+} signals [18]. Cells are thereby protected against apoptosis by a more sensitive coupling of the ER to mitochondria that enhances cellular bioenergetics [18].

The results discussed above suggest that normal ER-to-mitochondria Ca^{2+} signaling should remain within a relatively small physiological range. Mitochondrial Ca^{2+} overload was for a long time recognized as a determinant in apoptotic and necrotic cell death and was related to the role of the mitochondrial permeation transition pore (PTP). The properties and crucial importance of this specialized mitochondrial structure is discussed in this Special Issue by A. Rasola and P. Bernardi. Persistent PTP opening is followed by mitochondrial depolarization and Ca^{2+} release, cessation of oxidative phosphorylation, matrix swelling with inner membrane remodeling, and eventually outer membrane rupture with release of cytochrome c and other apoptogenic proteins [7]. On the other hand, sufficient Ca^{2+} supply by constitutive activity of

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the IP_3R is needed to provide Ca^{2+} to the mitochondria for efficient oxygen consumption and ATP production [23,24]. In the absence of this Ca^{2+} transfer, cells are prone to activation of autophagy to sustain their survival [23]. Autophagy is a process activated in stress situations, such as nutrient starvation, in which cells catabolize themselves to temporarily escape cell death [25,26]. The contribution of JB. Parys and colleagues in this Special Issue focuses on the emerging inter-relation of autophagy and Ca^{2+} signaling. The intimate relation between the ER and mitochondria also implies that ER stress is directly sensed by the mitochondria, and several cell death mechanisms are induced by ER stress [27]. The evolutionary conserved Bax Inhibitor-1 (BI-1) family of anti-apoptotic proteins, which is not related to the Bcl-2 family, may play an important role in protection against ER stress and ER-stress-associated cell death [28]. BI-1 is strongly upregulated in neurons in conditions of oxidative stress [29] and protects against stroke and traumatic brain injury [30], as is outlined in the review by A. Methner and colleagues in this Special Issue. One of the canonical inducers of ER stress is the inhibition of the Ca^{2+} sequestration by thapsigargin. The activity of Ca^{2+} pumps is therefore an intrinsic part of the control of cell death via the ER, and inhibition of the ER Ca^{2+} pump may be a target for forcing cancer cells into necrosis [8,31]. On the other hand, the active Ca^{2+} transporters in the plasma membrane, the plasma membrane Ca^{2+}-ATP as pump (PMCA) [32] and the Na^+/Ca^{2+} exchanger [33] are down-stream targets of caspase-3 and together with the caspase-3-dependent cleavage of the IP_3R [34–36], they constitute a positive feedback system in a late apoptotic phenotype.

Although the ER–mitochondria connection has attracted much attention, there is good evidence that Ca^{2+}-influx mechanisms at the plasma membrane that are directly or indirectly coupled to store depletion, are very important for cell fate. Physiological Ca^{2+} influx is essential for cell survival by virtue of all the cellular responses mediated by Ca^{2+} from gene regulation to neurotransmission. Ca^{2+} influx is required to maintain all forms of Ca^{2+} signals from puffs to oscillations to Ca^{2+} waves [37]. Yet, excessive Ca^{2+} influx is highly toxic leading to cell death. This has been widely documented for cell death programs in neurons [38,39], and in blood cells [10,40,41]. Ca^{2+} toxicity and cell death due to Ca^{2+} influx activated by excessive receptor stimulation and by other cell stressors is a nodal point in inflammatory diseases such as pancreatitis and Sjögren's syndrome [42,43]. The sustained increase in Ca^{2+} influx and cytoplasmic Ca^{2+} leads to aberrant membrane trafficking and apoptosis that is followed by necrosis and irreversible tissue damage. The dual role of Ca^{2+} in cell survival and cell death is highlighted in this Special Issue attention by contributions focused on T-cell survival by M. Hoth and colleagues, and on the role of STIM/ORAI1 signaling in platelets by B. Nieswandt and colleagues.

There is also increasing evidence for a role of members of the transient receptor potential (TRP) superfamily in different aspects of cell death. The role of TRPC channels in cell death was documented in several pathological conditions [44,45]. Moreover, members of the TRPM subfamily have been invoked as mediators of oxidative stress. Ca^{2+} influx via TRPM7 is important for anoxic neuronal death [46,47]. As outlined by Y. Mori and colleagues in this Special Issue, TRPM2 is a nonselective Ca^{2+}-permeable cation channel with an established role in cell proliferation and oxidant-induced cell death [47,48]. In addition to its role as a plasma membrane channel, TRPM2 also functions as a Ca^{2+}-release channel activated by intracellular ADPR in a lysosomal compartment. Both functions of TRPM2 are critically linked to hydrogen peroxide-induced beta cell death [49]. Several other TRPs also have an established localization in intracellular membranes and interfere with cell death via organellar Ca^{2+} fluxes. This is particularly the case for the differentiation-dependent localization of TRPM8 and its role in prostate cancer [50]. A very remarkable intracellular function is found for the TRPML subfamily in the regulation of membrane and protein sorting along the endo-lysosomal pathways and starvation-induced autophagy [51]. Defective clearance of apoptotic cells was related to mucolipidosis type IV in a Drosophila model [52]. The role of these metal ion transporters in the lysosomes is further outlined by S. Muallem and colleagues.

Dysfunctions provoking either a defect in cell death or exaggerated cell death have severe acute and chronic pathological consequences. The role of aberrant Ca^{2+} influx in acute inflammatory diseases is well established (see review by B. Zhivotovsky and S. Orrenius). Targeting apoptosis has become an attractive therapeutic strategy in the treatment of cancer, which is often associated with resistance to apoptosis [53]. Due to its anti-apoptotic and oncogenic function in cancer cells, Bcl-2 became an important target for anti-cancer therapy, particularly for small-molecule Bcl-2 inhibitors that target the hydrophobic cleft [54]. An alternative strategy could be presented by targeting Ca^{2+} signaling as a mediator of Ca^{2+}-dependent cell death [55,56]. In this respect different types of Ca^{2+} transporters [57], particularly IP_3Rs [58] and some types of TRP channels [59] may play an important role. Different contributions in this Special Issue particularly by C. Distelhorst and M. Bootman, and by N. Prevarskaya and colleagues, deal with different aspects of cell death in cancer pathology. Cell death is not restricted to one cell, but intercellular junctions mediate spreading of cell death to neighboring cells, a mechanism that could be very important in targeting cancer cells as is further discussed in a contribution by L. Leybaert and colleagues [60,61]. Exaggerated or inappropriate cell death consistently leads to severe pathologies including particularly neurodegenerative diseases [62] and normal aging [63,64]. Anomalous neuronal Ca^{2+} signaling and its consequences for neuronal cell death is discussed by C. Supnet and I. Bezprozvanny in this Special Issue.

Cell death pathways mostly implicate a profound remodeling of the Ca^{2+}-signaling toolkit. It is increasingly evident that very accurate fine tuning of the cellular Ca^{2+} fluxes is required for cell survival, and malfunction of the Ca^{2+} signaling machinery may lead to exaggerated or defective cell death both resulting in severe pathologies. Preventing and perhaps correcting aberrant Ca^{2+} signaling is thus a very promising target for developing therapy for several acute and chronic diseases from inflammation to metabolic diseases to cancer to neurodegenerative to cardiac diseases, components of all of which are strongly associated with aberrant Ca^{2+} signaling.

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